Case Reports

Acute Pancreatitis Associated With Long-term Sulindac Therapy

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SULINDAC (Clinoril, Merck Sharp & Dohme, West Point, Pa), a nonsteroidal anti-inflammatory agent, is widely used in the treatment of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis and other rheumatic disorders.[1] Its use has been associated with a variety of adverse reactions, including gastrointestinal toxic reaction,[2,3] hepatotoxic disorder,[4,5] hypersensitivity reactions,[3] aseptic meningitis,[6] Stevens-Johnson syndrome,[5] toxic epidermal necrolysis syndrome,[5] agranulocytosis,[7] aplastic anemia[8] and acute pancreatitis.[2,5,9-11] Many of these untoward effects occur early in the course of therapy. We describe a case of acute pancreatitis associated with long-term sulindac therapy.

Report of a Case

The patient, a 31-year-old woman with the diagnosis of polyarticular juvenile rheumatoid arthritis since age 11, had been receiving ongoing nonsteroidal anti-inflammatory therapy with sulindac, 150 mg three times a day, since January 1979. In September 1984 nausea and epigastric pain developed that radiated to the back and she sought medical attention at a hospital emergency room where her serum amylase measured 2,547 units per dl. She was then transferred to the University of Utah Medical Center (UUMC). The patient had no history of biliary or peptic ulcer disease and did not drink alcohol. There was no history of abdominal trauma. The only other medication on admission was cyclobenzaprine hydrochloride, 10 mg, as needed for muscle spasms. She had received no steroid therapy for more than six years. The sulindac therapy was discontinued at the time of her admission to hospital. Serum aminotransferase and alkaline phosphatase levels at the time of admission were within normal limits and the serum amylase level fell to 191 units per dl (normal 23 to 85) by day 4 of her hospital course. An ultrasound study of the gallbladder and pancreas showed no abnormalities. The patient had increasing joint pain during her hospital stay and sulindac therapy at the previous dosage was reinstituted before discharge.

About six weeks later epigastric pain again developed with radiation to the back. A serum amylase determination at another hospital emergency room showed a concentration of 350 units per dl, and a diagnosis of acute pancreatitis was made. The patient was given meperidine hydrochloride intramuscularly and discharged. Because of persistent abdominal pain, she was subsequently admitted to UUMC at which time a serum amylase level was 1,122 units per dl and lipase was 800 IU per liter (normal 40 to 240). Also elevated were the following: total bilirubin 1.4 mg per dl (normal 0.2 to 1.3), γ-glutamyl transpeptidase 95 IU per liter (normal 5 to 85), alkaline phosphatase 203 IU per liter (normal 44 to 147) and aspartate aminotransferase 77 IU per liter (normal 9 to 55). The triglyceride level was normal, as was the serum calcium. An ultrasound study of the gallbladder showed no evidence of cholelithiasis or pancreatic abnormalities. An upper gastrointestinal series was attempted but could not be completed due to lack of patient cooperation. The patient's epigastric pain on admission resolved with the discontinuation of sulindac therapy, intravenous administration of cimetidine, fluids and bowel rest. Discharge values of serum amylase and lipase were 76 units per dl and 200 IU per liter, respectively. Treatment with the nonsteroidal drug piroxicam was started before discharge, which was later changed to ibuprofen, 600 mg four times a day, when an erythematous macular rash developed. No further episodes of acute pancreatitis have occurred in eight months.

ABBREVIATIONS USED IN TEXT
NSAID = nonsteroidal anti-inflammatory drug
UUMC = University of Utah Medical Center

Comment

Sulindac is frequently used in the treatment of rheumatic disorders. It is currently the 5th leading retail nonsteroidal anti-inflammatory drug (NSAID) (by volume in dollars) and overall the 18th leading retail drug.[12] As is the case with all NSAIDs, sulindac therapy is occasionally compromised by adverse gastrointestinal effects. Gastrointestinal reactions including abdominal pain, nausea, dyspepsia and constipation occur in 17% of patients taking the drug.[1] For many patients, therapy is discontinued because of these symptoms. While most of these problems result from gastric mucosal injury,[13] a few patients have had pancreatitis.[2,5,9-11] A spokesperson from Merck Sharp & Dohme confirms that the company has received about 100 reports of acute pancreatitis associated with sulindac therapy (oral communication, March 1985).

In this case, there is a strong correlation between the use of sulindac and acute pancreatitis given the recurrence of pancreatitis on readministration of sulindac and the lack of abuse of alcohol or use of other medications associated with acute pancreatitis. In addition, there was no evidence of biliary tract disease on two ultrasound examinations. A transient elevation of liver enzymes with the second admission may be attributed to pancreatitic swelling, drug-induced hepatitis or another unrelated mechanism. The patient did not have hypercalcemia or hyperlipidemia. The lack of evidence of peptic ulcer disease argues against this problem as causing the pancreatitis despite the inability to visualize the upper gastro-

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intestinal tract. At least two other NSAIDs have been given without subsequent abdominal pain, although piroxicam therapy was withdrawn because of a skin rash.

Sulindac is a drug that can cause acute pancreatitis. The literature reveals numerous medications that can induce acute pancreatitis, including azathioprine, thiazides, sulfonamides, furosamide, estrogens and tetracycline.[14] Other drugs such as indomethacin, opiates, salicylates and acetaminophen have been implicated as possible causes of pancreatic inflammation. Four of the previously reported cases of sulindac-induced pancreatic disease[2,5,10,11] included readministration of sulindac, with recurrence of the pancreatitis, as also occurred in the current case.

In all previous reports of sulindac-induced acute pancreatitis, the adverse reaction is an early phenomenon. Symptoms developed in all previous patients within six months of the beginning of sulindac therapy. Our case is unique in that acute pancreatitis did not appear until after more than five years of therapy. This suggests that acute pancreatitis is not necessarily an early complication of sulindac usage but must be considered in any patient receiving sulindac in whom gastrointestinal complaints develop.

Sulindac will continue to be a useful medication for the treatment of rheumatic diseases. As with all NSAIDs, caution must be taken to identify untoward gastrointestinal reactions that may result in gastric ulceration or hemorrhage. While gastrointestinal complaints are common and acute pancreatitis is uncommon, the latter must be considered in any patient taking sulindac in whom abdominal pain, nausea or vomiting develops. A long duration of therapy does not exclude the possibility of acute pancreatitis.

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Near-Fatal Coagulopathy Associated With Epstein-Barr Virus Hepatitis

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PATIENTS with acute infectious mononucleosis are infrequently admitted to hospitals and fatalities are rare. Of those admitted, serious complications develop in less than 5%.[1] Although several fatal cases of suspected mononucleosis were reported in earlier years, by 1970 only 20 well-documented fatal cases with serologic, hematologic and clinical evidence of infectious mononucleosis had been reported to the Centers for Disease Control.[2] Causes of death in order of decreasing frequency were neurologic complications, splenic rupture, secondary infection, hepatic failure and myocarditis. The number of fatal cases has recently increased in the United States and it is estimated that 30 to 35 now occur per year.[3] This probably is due to greater appreciation of the seriousness of Epstein-Barr virus (EBV) infection.

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In the patient presented here, severe hepatocellular dysfunction developed with persistent hypofibrinogenemia and near-fatal hemorrhaging. Cryoprecipitate therapy resulted in substantial improvement in clinical state. We also review the literature on hepatic failure in EBV-associated infectious mononucleosis and suggest an approach for evaluating hemorrhagic complications when severe liver injury is present.

Report of a Case

The patient, an 18-year-old male student, was admitted to the University of Arizona Health Sciences Center for spontaneous bleeding from the left tonsil, jaundice and malaise. He had noted a sore throat, headache and fever 11 days earlier. One week later, he had become anorexic and glandular neck swelling developed. He was found to have a positive screening heterophil antibody (Monospot) test and leukocytosis with 15,200 cells per μl, including many atypical lymphocytes. Bleeding from the left tonsil developed three days before admission. The tonsil was cauterized then and again 48 hours later. In addition, he was clinically jaundiced. There were elevations in the serum bilirubin level to 9.3 mg per dl, the serum aspartate aminotransferase (AST, formerly SGOT) level to 450 IU per liter, the serum alanine aminotransferase (ALT, formerly SGPT) level to 377 IU per liter and the alkaline phosphatase level to 498 IU per liter. Despite one further cauterization, profuse bleeding from the left tonsil continued and he was admitted. An initial dose of prednisone, 80 mg, was given orally.

The past medical history was remarkable for severe systemic toxoplasmosis at the age of 5. There was no previous history of blood product transfusion, intravenous drug use, excessive alcohol intake, homosexual activity, hepatitis or bleeding disorders. There was no family history of severe